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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,407	09/12/2001	Hugo R. Rosen	6915-66815	1602

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EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,407	ROSEN, HUGO R.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,7-15,17,19-24 and 35-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,8-15,17,20-24 and 35-38* is/are rejected.

7)☒ Claim(s) *7,19 and 35-40* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 5, 7-15, 17, 19-24 and 35-40 are pending in the application.

This Office Action is in response to the Amendment filed on 10/30/2003.

Response to Amendment

The rejection of claims 8-10 and 13-24 under 35 U.S.C.112 2nd paragraph has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 1-3, 5, 8-15, 17, 20-24 under 35 U.S.C.112 1st paragraph (written description and scope of enablement) is maintained for reasons set forth of the record mailed on and further discussed below.

Claims 35-38 are rejected under 35 U.S.C. 112 2nd paragraph for reasons discussed below.

Claims 7, 19, 35-40 are objected to for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 8-15, 17, 20-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In response to this rejection, Applicant argues that the specification (page 13 line 13 to page 13, line 34) identifies polymorphic sites, other than TNF-α, in genomic nucleic acid encoding IL-1, IL-2, IL-6, IL-8, TGF-β, IL-10, GMCSF and CNTF. Furthermore, Applicant argues that the amended claims only refer to polymorphisms in genomic sequence encoding these cytokines. Applicant thus concludes that the amended claims satisfy the written description requirement.

This argument has been fully considered but is deemed unpersuasive. The specification only prophetically discloses that polymorphisms in IL-1, IL-2, IL-6, IL-8, TGF-β, IL-10, GMCSF and CNTF that would decrease the expression or activity of TNF-α is a preferred donor type because the polymorphism at –308 in TNF-α is correlated with reduced incidence of hepatitis C recurrence in liver transplantation, and such polymorphism results in low expression of TNF-α. However, the specification fails to describe what type of polymorphisms of these cytokines is correlated with decreased TNF-α expression and reduced incidence of hepatitis C recurrence after liver transplantation. The specification also fails to describe other polymorphic site(s) within TNF-α, either in the regulatory region or coding region, would result in the reduced incidence of hepatitis C recurrence after liver transplantation. On the contrary, the specification discloses "there is no correlation between TNF-β alleles and time of recurrence, severity of recurrence or prevalence of rejection (see page 28, top paragraph)." As such, the structural functional relationship between the polymorphic sites in IL-1, IL-2, IL-6, IL-8, TGF-β, IL-10, GMCSF, CNTF and reduced incidence of hepatitis C recurrence (HCR), thus preferred donor genotype, is missing. Thus, the written description requirement is not met because the

specification does not describe a representative number of species by their complete structure or other identifying characteristics. Therefore, this rejection is maintained.

Claims 1-3, 5, 8-15, 17, 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a preferred liver donor for transplantation to a recipient infected with hepatitis C virus comprising determining in the donor tissue the presence of a preferred genotype, wherein said genotype is polymorphism at nucleotide position –308 in the TNFα promoter, wherein a G is at said position, does not reasonably provide enablement for a method of identifying a preferred liver donor for any recipient by identifying a preferred genotype in said donor, wherein said genotype is a polymorphism at any site in the genome that is associated with altered activity of any tumor necrosis factor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In response to this rejection, Applicant argues that the specification provides full enablement for methods for determining polymorphisms in the regulatory regions in IL-1, IL-2, IL-6, IL-8, TGF-β, IL-10, GMCSF, CNTF genes. Applicant further argues that the specification (page 13, lines 13-34) teaches genes and preferred genotypes associated with expression of these genes. Moreover, Applicant argues that methods for detecting specific polymorphisms are provided in the specification (page 19, line 26 to page 25, line 3). Applicants further cited Tambur et al. to demonstrate that 1) the polymorphisms in TGF-β and IL10 are identified and known in the art; 2) there is an association between polymorphisms of TGF-β and IL-10 with recurrence of hepatitis C in liver transplant recipients. Applicant points out that the specification discloses that a genotype at a polymorphic site that is associated with activity of TGF-β or IL-10

is a preferred genotype (page 13, 27-29, and page 13, lines 29-32). Applicant argues that based on the teaching of the specification, Tambur et al. analyzed known polymorphisms in TGF-β, IL-10 and conclude that the high levels of TGF-β or low level of IL-10 are preferred genotypes, thus demonstrates that the guidance provided by the specification, one of skill in the art could readily use polymorphisms in the TGF-β or IL-10 to identify a preferred liver donor.

These arguments have been fully considered but deemed unpersuasive. As discussed in the previous office action, although polymorphisms in cytokine genes are known in the art at the time of filing, it is unpredictable which polymorphic site(s) are correlated with reduced incidence of rejection or recurrent disease post liver transplantation. Although the specification teaches how to identify polymorphisms in the regulatory regions of IL-1, IL-2, IL-6, IL-8, TGF-α/β, IL-10, GMCSF, CNTF genes, it does not provide teaching that would overcome the unpredictability discussed in the art. On the contrary, the specification teaches that polymorphisms in TGF-β are not correlated with recurrent hepatitis C infection (see page 28, top paragraph). Thus, the specification does not provide sufficient guidance for the full enablement of the claimed inventions.

With regard to the teaching of Tambur et al., Applicant is reminded that the claimed invention must be enabled at the time the application was filed. Tambur et al. was published two years later than the priority date of the instant specification. Moreover, Tambur et al. indicate that numerous studies in which cytokine gene polymorphism was analyzed in relation to allograft rejection or other transplantation complications disputed earlier findings and revealed many controversies (see page 1478, bridging paragraph of col. 1 and 2). Tambur et al. further point out that their finding is contradictory to an earlier report that TNF-α 308 (A/A) genotype is more

likely to develop HCR (see page 1478, last paragraph). Moreover, Tambur et al. state that "the multifactorial nature of post transplant immune responses, especially in the early post liver transplant period complicate our ability to differentiate the role and contribution of individual parameters for the development of rejection." Therefore, despite Tambur et al's findings of an association between a specific genotype within TGF-β, IL-10 and HCR, whether a single or combination of polymorphic site within any of the claimed cytokine genes is correlated with post liver transplant rejection is unpredictable. Furthermore, whether a single or combination of polymorphic site within any of the claimed cytokine genes indicates a preferred donor type is unpredictable. The data presented in Tambur et al. is based on empirical experimentation, rather than routine experimentation. Therefore, the claimed invention is not enabled to its full scope.

New Grounds of Rejection Necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35-38 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "at position –380" renders the claims indefinite because it is unclear what is the reference point for position –380. In other words, it is unclear if the –380 is relative to transcription start site, translation start site or other position(s). The specification discloses a polymorphic site at position –308 relative to transcription start site.

Claim Objection

Claims 7 and 19 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Double Patenting Warning

Applicant is advised that should claims 7, 14, 19 and 24 be found allowable, claims 35-40 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER